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FOREWORD

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Introduction

There is a growing body of epidemiological literature supporting the positive relationship between a woman's endogenous lifetime hormone exposure and the risk of breast cancer¹⁻³. Specifically, early menarche and late menopause are associated with increased risk of breast cancer, and this risk is reduced by surgical oophorectomy in the premenopause. Breast cancer adjuvant treatments often lead to premature menopause, and this may be an important factor in the efficacy of these treatments in younger women^{4,5}. However, women who experience premature menopause are at increased risk of earlier cardiovascular disease, as well as premature osteoporosis. There is uncertainty about how all of these factors play out in breast cancer survivors who have experienced premenopausal breast cancer, and may become prematurely menopausal as a result of their treatment. Therefore, the primary focus of this cross-sectional study is to examine gonadal function and reproductive health comprehensively in long-term survivors of breast cancer.

Specific Aims

1. To recruit a sample of breast cancer survivors (BCS) who were 50 years or younger at diagnosis, and were treated initially at the Jonsson Comprehensive Cancer Center at UCLA between 1994 and 1997, to complement a prior study of similar women treated between 1989 and 1994. (Phase One)
2. To recruit additional subjects with identical characteristics treated at Kaiser Permanente West Los Angeles or Kaiser Permanente Sunset between 1989 and 1997. (Phase One)
3. To survey these BCS to determine the effects of past treatment on menstrual history patterns and fertility, as well as past and current menopausal symptoms, and current health-related quality of life. (Phase One)
4. To measure current reproductive hormone status, cardiovascular lipid profiles, body composition and bone mineral density (BMD) in these BCS to assess the late effects of breast cancer treatment on risk factors for coronary artery disease and osteoporotic fractures. (Phase Two)
5. To measure neurocognitive functioning in these BCS to examine whether a relationship exists between various domains of cognitive functioning and type of adjuvant therapy received. (Phase Three)
6. To measure longitudinal BMD in these BCS, 18 months after the initial BMD in Phase Two, to examine if group differences exist among women who received different types of adjuvant therapy. (Phase Four)

Description of Phases 1, 2, 3 and 4

The study was conducted in four phases. In phase one, the UCLA Medical Center Tumor Registry and the Kaiser Permanente Tumor Registry were used to identify a group of breast cancer survivors who were 50 years or younger at the time of diagnosis and who were disease free at the time of recruitment. Eligible BCS were invited to participate in study and were asked to complete a survey questionnaire that reviewed their menstrual and reproductive history, medication history (including past and current use of contraceptive and non-contraceptive hormones), pregnancy/fertility history, past and current symptoms that may be menopause related, use of alternative therapies, diet and physical activity levels, as well as standardized measures of health-related quality of life. The survey also asked detailed information about each subject's cancer treatment, including type and duration of chemotherapy and hormone therapy received. In addition to analyzing the results from the survey, we examined the medical and demographic characteristics of breast cancer survivors who participated in comparison with those who refused.

In phase two of the research, all BCS who completed the phase one survey questionnaire were invited to come to UCLA for an in-person visit to complete physical and laboratory studies. These included blood work for evaluation of cardiovascular lipids and gonadal hormones; measurement of blood pressure, height, weight and waist/hip girth, and performance of a bone mineral density test (BMD). The results of the questionnaire data and medical treatment details from phase one, as well as current gonadal hormone levels, will be used to explore the predictors of current health status/health-related quality of life, cardiovascular lipids, and bone mineral density. The analyses planned will examine whether a relationship exists between menstrual patterns after breast cancer and current health-related quality of life, lipid profiles, bone mineral density or body composition. These data will be useful in the management of women who are currently long-term survivors of breast cancer, and can be used to provide supporting pilot data for the design of a prospective longitudinal study examining the impact of breast cancer treatment on the long-term reproductive health of premenopausal women with breast cancer.

Since our original study was designed, we added two additional components - a study of neurocognitive functioning (phase three) and a longitudinal follow-up study of bone density (phase four). In phase three of the research, women between 2 and 5 years post-diagnosis who completed phases one and two and who met other eligibility criteria were invited to come to UCLA for an in-person visit to complete a battery of neurocognitive functioning tests. In addition to the neurocognitive tests, we collected saliva samples for cortisol, performed a single blood draw for immune function studies, as well as measured blood pressure and heart rate. We eventually discontinued collecting saliva samples, because 1) a preliminary analysis of cortisol levels during and after testing showed no stress effect, and 2) by eliminating saliva collection, we were able to reduce the appointment time from four hours to 2.5 hours, thus reducing subject burden. We also invited women with no history of breast cancer to participate as control subjects for this phase of the study. The main analysis, which was completed in this reporting

period, examined whether a relationship exists between cognitive functioning and type of adjuvant therapy received (chemotherapy alone; both chemotherapy and tamoxifen; or no therapy). We also compared neurocognitive functioning between breast cancer survivors and women with no history of breast cancer. The blood measurement was for examination of immune functioning.

In phase four of the research, women who completed phase two were invited back to receive a follow-up bone mineral density at 18 months after the initial bone density study. We added this phase to examine whether observed differences from the cross-sectional evaluation persisted over time. We plan to compare group data between the initial and the follow-up BMDs.

Progress report on fourth year (no cost extension period)

Final data collection for the follow-up bone density study (phase four) was completed in May, 2002, when we approached the last remaining eligible subjects. Assays of hormones from phase two were finalized in August, 2002. Because of this extended period of data collection and finalization, we have requested an additional year of no-cost extension to complete the analyses of the study data. Therefore, this is a progress report rather than a final report.

Recruitment and Subject Characteristics

Data collection for phase one was completed in the previous reporting period. Of the 1084 invitation letters sent, we were able to make subsequent contact with 765 (71%) of the women to ascertain interest in the study. Of these 765 reachable women, 580 (76%) agreed to participate in the study. Among the 580 interested women, 44 (7.5%) women were found to be ineligible, 2 women refused during the telephone screening process, and 404 (70%) women successfully completed the questionnaire.

Also completed in the last reporting period was data collection for phase two, in which we approached women who completed a questionnaire and who lived in California to come in for an in-person visit, which included a blood draw to measure cholesterol and hormone levels, and a DEXA scan to measure bone mineral density. Of the 392 invitation letters sent for this phase of the study, 375 (96%) of the invited women were reachable by phone. Of these women, 116 (31%) were not interested in participating. Of the remaining 259 women, 15 (6%) were deemed ineligible because they were not currently cancer-free; 4 shared data from an unrelated visit; and 240 women completed the appointment.

Recruitment for phase three was completed in this reporting period. Since March 2000, we sent a total of 134 invitation letters to short-term BCS to come to UCLA for a battery of neurocognitive tests. Of these 134, we were able to make subsequent contact with 123 (92%) women, 70 (57%) of whom were interested in participating. Of the 70 interested women, 11 (16%) were found ineligible during screening, 4 (6%) women refused to schedule an appointment, and the remaining 55 were eligible and successfully

completed their appointments. In this reporting period, we also completed recruitment of control subjects for this phase of the study. A total of 21 control subjects completed the study, however two of them were subsequently found ineligible. Therefore, our final sample for phase three of the study includes 55 breast cancer survivors and 19 control subjects.

Recruitment for phase four was also completed in this reporting period. Between October 1, 2001 and January 9, 2002, we sent invitation letters to 75 more women who were 18 months past their initial BMD to invite them to come in for a follow-up BMD. Altogether, a total of 152 invitations were sent for this phase of the study. Among the 134 (88%) women we were able to make subsequent contact with, only 15 (11%) were not interested. Twelve (9%) women were not eligible because they were not currently cancer free. All of the remaining 94 women who were both eligible and interested have completed their appointments.

Additional Data Collection

The recruitment numbers reported for phases one, two and four above contain only those subjects recruited with DOD funding for this particular study. However, this DOD funding was in fact used to expand on prior data already collected by a similar study that was initiated with NCI funding. Therefore, in addition to the data collected on the subjects described above, we have phase one questionnaire data on an additional 173 long-term survivors (5-10 years since diagnosis), as well as phase two biologic and bone density data on 103 of these women, and phase four bone density data on 71 of these women. For all analyses, we will combine data from both the NCI and the DOD studies.

Data Analysis

We have now completed data collection for all phases of the study. We have questionnaire data from phase one on a total of 577 breast cancer survivors, and bone density and biologic data from phase two on a total of 346 of these women. We also have neurocognitive functioning data on 74 women from phase three, and 18-month follow-up bone density data on 165 women from phase four.

In the middle of this reporting period, Carolyn Crandall, M.D., applied for and received a New Investigator award from the California Breast Cancer Research Program. This is a three-year award which began on July 1, 2002, and which provides funding for Dr. Crandall to develop her research skills through participating in analyses from this study. Dr. Crandall is being mentored by Drs. Ganz and Greendale, and has already begun work on writing a descriptive paper about phase one of the study. Her subsequent analyses will involve data from phases two and four of the study. A lay abstract from Dr. Crandall's award application is included in this report as the appendix. In addition, Dena Herman, Ph.D., has joined our team as an NCI-funded post-doctoral fellow, and she will be working with Drs. Ganz and Greendale to examine changes in body composition (from DEXA scan data) related to adjuvant therapy. We expect that participation of these two

post-doctoral trainees in the analysis of these data will foster their long-term involvement in breast cancer research.

In this reporting year, Dr. Steven Castellon analyzed the phase three data. He reported on his results at the 21st Annual Meeting of the National Academy of Neuropsychology in San Francisco in November, 2001. An abstract of his presentation appeared in the Archives of Clinical Neuropsychology. In addition to his presentation, Dr. Castellon has submitted a paper with his findings to the Journal of the International Neuropsychological Society.

Key Research Accomplishments

- In phase three of the study, three groups of women completed a neurocognitive battery evaluating memory, attention, motor speed, reaction time, visuospatial and executive function and current mood. The three groups of women were: BCS with no adjuvant therapy; BCS who had adjuvant therapy (either chemotherapy alone or chemotherapy and tamoxifen); and normal healthy control women. Dr. Castellon found that those BCS who received adjuvant chemotherapy performed significantly worse in the domains of verbal learning, visuospatial functioning and visual memory than BCS not exposed to such therapy. Those BCS who underwent chemotherapy and also used tamoxifen were most likely to evidence cognitive compromise. Those BCS who received no adjuvant therapy appeared to perform as well, and in some cases, better than demographically matched healthy controls. Additionally, self-reported cognitive complaints were not related to objective performance on neurocognitive tasks, although poor cognitive performance was significantly correlated with self-reported mood disturbance (both depression and anxiety) as well as self-reported fatigue.

Reportable Outcomes

- Manuscript: Castellon, SA, Ganz, PA, Bower, JE, Petersen, L, Abraham, L, Greendale, GA. Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. Submitted to the Journal of the International Neuropsychological Society. Submitted in September, 2002.
- Abstract and Presentation: Castellon, SA, Ganz, PA, Abraham, L, Bower, JE, Pakilit, AT, Petersen, LP, Greendale, GA. Neurocognitive performance in breast cancer following exposure to adjuvant systemic therapy. Paper presented at the 21st annual meeting of the National Academy of Neuropsychology, San Francisco, CA, November, 2001. Abstract to appear in Archives of Clinical Neuropsychology.
- Editorial: Ganz, PA, Castellon, SA and Silverman, D. (2002) Estrogen, tamoxifen, and the brain. Journal of the National Cancer Institute, 94: 547-549.

- Funding received based on work supported by this award: Dr. Carolyn Crandall received a New Investigator award from the California Breast Cancer Research Program entitled, "Impact of Breast Cancer and its Therapy on Osteoporosis." The award is for three years, starting July 1, 2002, and will allow Dr. Crandall to analyze data from this study, under the mentorship of Drs. Ganz and Greendale.
- Funding received based on work supported by this award: Dr. Dena Herman received a post-doctoral trainee award from the UCLA Cancer Education and Development Program, which is funded by the NCI. This award is for two years, starting in September, 2002, and will allow Dr. Herman to analyze data from this study, under the mentorship of Dr. Ganz.
- Funding received based on work supported by this award: Dr. Ganz was awarded a grant from the Breast Cancer Research Foundation for "Neuroimaging Correlates of Cognitive Dysfunction After Breast Cancer Treatment." This grant was awarded on October, 2002, for two years.
- Funding applied for based on work supported by this award: Dr. Ganz and Dr. Castellon have re-applied for a DOD Idea Award entitled "Innovations in the Evaluation and Detection of Cognitive Dysfunction in Breast Cancer Survivors."

Conclusion

In this funding year, we completed subject recruitment for all phases of the study. A paper about the effect of adjuvant chemotherapy and tamoxifen on cognitive functioning has been submitted to the Journal of the International Neuropsychological Society, and these findings were presented by Dr. Castellon at the 21st Annual Meeting of the National Academy of Neuropsychology. Dr. Crandall and the team have begun work analyzing phase one of the study.

In the upcoming year, we plan to complete the analyses for all phases of this project. Dr. Crandall plans to complete her paper describing the phase one sample, looking at differences in menstrual history patterns and fertility, as well as past and current menopausal symptoms, and current health-related quality of life among women in the four adjuvant therapy groups. The team also plans to analyze the longitudinal bone density data from phases two and four, and look at the correlation between estradiol and bone density. We will also examine data related to lipids, anthropometric measures, physical activity, and body composition in the entire DEXA scan sample and in those who participated in phase four.

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APPENDIX

Lay Abstract from Dr. Carolyn Crandall's New Investigator Award application from the California Breast Cancer Research Program:

Non-technical introduction to the research topics:

Survival of women with breast cancer continues to improve. Thus, breast cancer survivors (BCS) must have more knowledge about how breast cancer and its treatment affect their long-term health. Menopause is a universal female event; consequences may include osteoporosis. Yet there is disturbing lack of information about how BCS experience menopause, whether BCS develop osteoporosis, and what can be done about it. This application seeks to: 1) allow a highly-qualified clinician to become a researcher in the field of menopause and osteoporosis in BCS; and 2) in the context of this training, to undertake specific research focussed on osteoporosis in BCS. The candidate will acquire the skills to continue work in the intersection between breast cancer, menopause, and long-term health.

The question(s) or central hypotheses of the research in non-technical terms:

1. Higher estrogen levels may put a women at higher risk of breast cancer, but at the same time might help her build better bone mass. Thus, do women with breast cancer start out with better bone health (higher bone density) than women without breast cancer?
2. Do women with breast cancer lose bone at different speeds after menopause compared to women without breast cancer?
3. Can blood hormone levels predict the rate at which BCS lose bone?

The general methodology in non-technical terms:

For career transition. The candidate will: obtain a Masters in Clinical Epidemiology; undertake a strong breast cancer mentoring program with Dr. Patricia Ganz, to obtain in-depth understanding of the how breast cancer and its therapy affects the health and well-being of women; undertake mentorship in research methods and osteoporosis with Dr. Gail Greendale. For primary research. To address the 3 questions outlined above, the candidate will be mentored in the conduct of 3 data analyses that focus on bone density in BCS. She will use already-collected data from the Cancer and Menopause study, an ongoing study of breast cancer survivors led by Drs. Ganz and Greendale.

Innovative elements of the project in non-technical terms:

The good news is that women are living longer after breast cancer treatment. The bad news is that many of their questions about long term health, particularly related to menopause, remain unanswered. This project is innovative in that it will train a clinical researcher who will focus her research career on this under-studied area of survivorship. The innovative multidisciplinary approach to the training and the research outlined here, as well as the unique breast cancer survivor data base available to the candidate, are also critical elements of the project.